Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-14, 16-18, 20-47 are pending in the application, with claims 1, 14, 32, 34, 36, 38, 40 and 41 are the independent claims. Claims 1-13, 16-18 and 32-46 are withdrawn from consideration. Claims 15 and 19 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 14, 20, 22, 26, 28, 30, and 31 are sought to be amended. Support for the amendment to claim 14 can be found, *e.g.*, in original claim 15 and 19 as filed, paragraphs [0168] to [0227] at pages 88-112 and Example 39 of the specification. The amendments to claims 20, 22, 26, 28, 30, and 31 address informalities in the claims and place them in better form for examination. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

The Examiner contends that claims 14-15 and 19-31 are not accorded benefit under 35 U.S.C. 119 and/or 120 of U.S. Provisional Appl. No. 60/463,649, filed April 18, 2003. The Examiner contends that claims 14-15 and 19-31 are not accorded benefit because the claims are rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure. The Examiner further

contended that claim 31 is not accorded benefit because compounds disclosed in the claim are not disclosed in Appl. No. 60/532,665.

Applicants respectfully disagree with the Examiner. The compounds recited in claim 31 are disclosed, *e.g.*, at page 5 of provisional Appl. No 60/532,665, filed December 29, 2003. In addition, in accordance with the restriction requirement, and not in acquiescence to the Examiner's 35 U.S.C. § 112, first paragraph rejections, Applicants have amended claim 14 and cancelled claims 15 and 19. Applicants' claims 14 and 20-30 are entitled to claim the benefit of provisional Application No. 60/463,649, filed April 18, 2003. Applicants note that support for claims 14 and 20-25 may be found in claims 10-19 as filed in Applicants' provisional Appl. No. 60/463,649 and throughout the specification. Support for claim 26-29 may be found, *e.g.*, at pages 63-68, paragraphs [0137-155] of provisional Appl. No. 60/463,649. Support for claim 30 may be found, *e.g.*, in claim 20 of provisional Appl. No. 60/463,649. Applicants respectfully assert, as set forth below, that pending claims 14 and 19-31 meet the requirements of U.S.C. § 112, first paragraph, and therefore are entitled to the benefit of the filing date of one or more of Applicants' provisional applications.

Objection to the Specification

The Examiner objected to allegedly improper demarcated trademarks in the specification. The Examiner contends that each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating the proprietary nature, and accompanied by generic terminology. The Examiner further objected to the use of hyperlinks in the specification.

Solely to advance prosecution, and not in acquiescence of the objection, Applicants have deleted the hyperlinks from the specification and have capitalized all trademarks. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

Objection to the Abstract

The Examiner objected to the abstract because it exceeds 150 words in length. Solely to advance prosecution, Applicants have amended the abstract so that it is less than 150 words in length.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Claim Objections

The Examiner objected to claims 14 and 15 and 19-31 as allegedly encompassing subject matter of a non-elected invention. In accordance with the restriction requirement, and solely to advance prosecution, Applicants have amended claim 14 to recite a Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) of SEQ ID NOs:1, 2, 3 or 8.

The Examiner further rejected claims 20 and 22 for the alleged omission of an article prior to the term "TRRAIP." Solely to advance prosecution and not in acquiescence of the Examiner's objection, Applicants have amended the claims to recite "said" before "TRRAIP."

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objections.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 19, 26-29 and 31 under 35 U.S.C. 112, second paragraph, as allegedly indefinite.

Specifically, regarding claims 26-29, the Examiner alleged that it is not clear how the "assay" according to claim 20 and 22 is characterized as comprising one of the labeled compounds as recited in claims 26 and 28. The Examiner contends that the claims fail to set forth an active process step requiring the use of one or the other of the compounds recited in the claims. The Examiner inquired, *e.g.*, how a gambogic acid-related compound having a detectable label is used in the process. Applicants respectfully traverse this rejection.

Solely to advance prosecution, and not in acquiescence of the Examiner's rejection, Applicants have amended claims 26 and 28 to recite an active step wherein the label is detected. Further, the specification describes "label" and "homogenous" and "heterogenous" assays as follows:

> "Label" is used herein to refer to any atom or molecule that is detectable and can be attached to a protein or test compound of interest. Examples of labels include, but are not limited to, radiolabels, fluorescent labels, phosphorescent labels, chemiluminescent labels and magnetic labels. Any label known in the art can be used in the present invention. As used herein, "homogenous assays" refer to assays in which all components are mixed together in the same phase. One example of a homogenous assay is where the components mixed together are all in solution. In contrast, "heterogenous assays" refer to assays in which a first component is attached to a solid phase such

> as a bead or other solid substrate and one or more additional components are in solution.

Specification, paragraph [0088] at p. 43-44. The specification, *e.g.*, at pages 89-103 further describes various assays. Applicants respectfully submit that a person skilled in the art understands what is encompassed by the process "wherein the label is detected" in the assays.

The Examiner alleged that recitation of "transferrin receptor protein" in claim 19 is indefinite because it fails to point out with the requisite particularity the identity of the protein. The Examiner suggested that the claim be amended to recite a particular amino acid sequence. In accordance with the restriction requirement, Applicants have amended claim 14 to recite a Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) of SEQ ID NOS:1, 2, 3 or 8.

The Examiner alleged that claim 31 is indefinite because it recites the limitation "said compound" and claim 14 recites two distinct types of compounds, *viz.*, "potentially therapeutic anticancer compounds" and "test compounds" and it is allegedly not clear which compound are referred to. Solely to advance prosecution and without acquiescing to the Examiner's rejection, Applicants have amended claim 31 to recite that the recited compounds are potentially therapeutic anticancer compounds.

Accordingly, based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 14, 15 and 19-31 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner alleges that claims 14 and 20-31 are drawn to any of a broad genus of Apoptosis Inducing Proteins (AIP) and monitoring whether said one or more test compounds bind to said AIP to identify potentially therapeutic anticancer compounds. The Examiner alleges that the specification fails to describe this genus and only describes with the requisite particularity one member of the genus of AIPs, *viz.*, the transferrin receptor protein. The Examiner contends that the genus of AIP members have substantial and significant variant structures and/or functions and that the specification fails to adequately describe the genus as a whole. The Examiner further alleges that the genus of Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) is not reasonably considered representative of the genus as a whole, since, *e.g.*, the specification fails to describe any one particularly identifying structural feature of transferrin receptor protein which is shared by other members of the genus and which correlates with any one common identifying functional feature.

The Examiner appears to have examined the original claim 14, notwithstanding the Examiner's requirement for restriction and the Applicants' election of a specific Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) for prosecution. In accordance with the restriction requirement, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 14 to recite a Transferrin Receptor Related

Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8. Accordingly, this ground of rejection is now moot.

The Examiner further rejected the claims on the grounds that the "mere ability of a test compound to bind an 'AIP' (e.g., 'transferrin receptor protein') does not alone provide an indication that the compound is capable of inducing apoptosis of cells expressing the protein, and wound not necessarily provide an indication that the test compound might be therapeutically useful in treating cancer." *Office Action* at p. 12. The Examiner contends that "it should not be considered sufficient to merely describe the test compounds to which the claims are directed as *perhaps* capable of binding the protein." *Id.* at p. 13. The Examiner acknowledges that Applicants have discovered that gambogic acid and structurally related compounds bind to the transferrin receptor and are capable of inducing apoptosis. The Examiner contends that the specification has not particularly described test compounds other than compounds related in structure to gambogic acid, which bind to transferrin receptor. The Examiner contends that the specification would amount to no more than a mere invitation "to discover the identity of other types of test compounds, which are not structurally related to gambogic acid."

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 14 to recite, *inter alia*, contacting Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8 and a detectably labeled gambogic acid (GA) or GA-related compound with one or more test compounds. According to the specification, Applicants have discovered, *inter alia*, that gambogic acid and related compounds are potential anticancer compounds that induce apoptosis and that these compounds bind to the transferrin receptor. Importantly,

Applicants have also discovered that the binding site of these compounds to the receptor is distinct from that of transferrin and have further discovered that internalization of the transferrin receptor can be interfered with by administration of the compounds. *See* Figures 1-2. Applicants have also correlated transferrin receptor levels and susceptibility to gambogic acid mediated apoptosis. *See* Figure 3. Applicants' results provide an apparent nexus linking transferrin receptor binding and the apoptotic effects of these compounds. Applicants' discovery further illuminates that the transferrin receptor, specifically the region(s) of the receptor to which the compounds bind and apparently effect blocking of internalization, is a novel target for identifying potentially therapeutic anticancer compounds. The claims are not directed to methods of detecting test compounds that bind to *any* region of the receptor. The claims are directed to identifying therapeutic anticancer compounds that are capable of competing for binding with gambogic acid (GA) or a GA-related compound to TRRAIP. Since the potentially therapeutic compounds are capable of competing for binding, there is an indication that the test compounds may be therapeutically useful in treating cancer. The Applicants' claim is directed to, *inter alia*, a method for *identifying* compounds that are capable of competing with gambogic acid (GA) or a GA-related compound. The specification shows that Applicants were in possession of a method of *identifying* compounds that are capable of competing for binding to the transferrin receptor with gambogic acid (GA) or a GA-related compound.

The Examiner further points out that the description of such compounds as having an ability to *affect* apoptosis implies that the compounds may have the ability to either promote or inhibit apoptosis, yet the specification only reasonably conveys

possession of compounds that bind to transferrin receptor and promote apoptosis and that there are no test compounds which have been particularly described as capable of inhibiting apoptosis. Applicants respectfully point out that while "affect apoptosis" appears throughout the specification, the language *does not* appear in the claims. The claims recite compounds as being "potentially therapeutic anticancer compounds." Since cancer is a disease of unchecked cell proliferation, inhibiting apoptosis would not have the desired anticancer effect. As correctly pointed out by the Examiner, the specification describes compounds that bind to transferrin receptor and promote apoptosis. Therefore, in view of the specification and the claim language, the only reasonable interpretation of the claim language vis-à-vis apoptosis is an effect of inducing apoptosis.

Based on the forgoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 14-15 and 19-31 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Applicants respectfully traverse this rejection.

The Examiner contends that while the specification indicates that the subgenus of TRRAIPS includes mutants, homologs, derivatives and fragments of "transferrin receptor protein," it does not particularly describe the structural modifications that can be made to the transferrin receptor protein without loss of function and that the artisan cannot predict whether any given protein is associated with apoptosis. The Examiner further contends that even in instances where a given protein is known to function in the process, the

artisan cannot predict whether the protein may be used to screen "test compounds" to identify those that are potentially therapeutic and that the amount of guidance, direction, and exemplification is not sufficient to reasonably enable the skilled artisan to make and then use any protein, other than transferrin receptor protein to screen test compounds to identify those having potentially therapeutic value. The Examiner further contends that while the claims are directed to any test compound, the specification only describes gambogic acid or GA-related compounds capable of binding transferrin receptor protein, so that the amount of guidance, direction and exemplification set forth in the specification is not reasonable commensurate in scope with the breath of the claims. The Examiner contends that unless a compound is structurally related to gambogic acid or other known ligands of the receptor, the skilled artisan could not reasonably predict whether the compound will be capable of binding the transferrin receptor protein. Applicants respectfully traverse this rejection.

In accordance with the restriction requirement, and solely to advance prosecution, Applicants have amended claim 14 to recite contacting a Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8 and a detectably labeled gambogic acid (GA) or GA-related compound with one or more test compounds. As discussed above, Applicants' discovery illuminates that the transferrin receptor, specifically the region(s) of the receptor that bind these compounds and effect blocking of internalization of the receptor, is a novel target for identifying potentially therapeutic anticancer compounds. The claims are not directed to methods of detecting test compounds that bind to *any* region of the receptor. The claims are directed to identifying therapeutic anticancer compounds that are capable of competing for binding

with gambogic acid (GA) or a GA-related compound to TRRAIP. Whether the test compounds are gambogic acid or GA-related is not at all critical to the invention. The Examiner appears to require that the claims recite only test compounds that are gambogic acid or GA-related compounds, so that it is *predictable* whether a test compound will bind the receptor. However, Applicants respectfully point out the claim is directed to a method of *identifying* compounds, and not a method of *predicting* compounds. If it were predictable which compounds would bind, there would not be much of a need to screen them. Persons skilled in the art of high-throughput drug screening are aware that thousands, even tens or hundreds of thousands of compounds can be routinely screened for binding to a suitable target molecule. There need not be any structural relationship whatsoever between the compounds that are being screened. Applicants have enabled the use of the transferrin receptor as a target for identifying compounds in screening assays. Applicants have also enabled methods of identifying potentially therapeutic compounds that are capable of competing for binding with gambogic acid (GA) or a GA-related compound to the receptor. Nothing more is needed to enable persons skilled in the art of drug screening to make and use this invention, commensurate in scope with the claims.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 14-15, 19-23 and 30 under 35 U.S.C. § 102(b) as allegedly anticipated by Faulk (U.S. Patent No. 5,000,935)("Faulk") as evidenced by Merino *et al.* (WO2004/009622 A2)("Merino *et al.*"). The Examiner contends that Faulk teaches contacting a transferrin receptor protein that is expressed on the surface of cells with a ^{125}I-transferrin bioconjugate and monitoring whether the bioconjugate binds to the transferrin receptor protein. The Examiner contends that this identifies the bioconjugate as a potentially therapeutic protein because the radiolabel is cytotoxic to the cells targeted. The Examiner contends that Faulk also teaches contacting the receptor with the conjugate *in vitro* and monitoring the binding, an assay which is considered a homogenous radioassay. The Examiner further contends that Faulk teaches contacting cells expressing a transferrin receptor in a xenograft mouse model with the ^{125}I-transferrin conjugate and monitoring whether the bioconjugate binds to the cells, which is allegedly a competitive assay system because the conjugate competes with naturally occurring transferrin. The Examiner cites Merino *et al.* as allegedly teaching that the transferrin receptor sequence is 100% identical to SEQ ID NOS:1, 2, 3 and 8. Applicants respectfully traverse the rejection.

Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have cancelled claims 15 and 19 and amended claim 14 to recite, *inter alia*, contacting a Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8 and a detectably labeled gambogic acid (GA) or GA-related compound with one or more test compounds. The specification demonstrates that binding of gambogic acid is not inhibited by binding of transferrin to

the receptor, strongly supporting that the binding sites for transferrin and gambogic acid are independent of each other. *See* Figure 1D of the specification. Faulk only disclose contacting a transferrin receptor with labeled transferrin and does not disclose contacting the receptor with a compound that competes with gambogic acid. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner rejected claims 14-15, 19, 22-23 and 30 under 35 U.S.C. § 102(b) as allegedly anticipated by Vaughan *et al.* (*In. J Radiation Oncology Biol. Phys.* 8:1943-1946 (1982)("Vaughan *et al.*"). The Examiner contends that Vaughn *et al.* teach an ^{211}At-transferrin receptor antibody bioconjugate and monitoring whether the antibody binds to transferrin receptor protein in a competitive heterogeneous assay comprising unlabelled antibody. The Examiner further contends that the antibody causes cell death in the cells targeted which identifies the antibody bioconjugate as a potentially therapeutic anticancer compound. Applicants respectfully traverse this rejection.

Applicants note there are no data in Vaughn *et al.* showing that the antibody binds to human transferrin receptor. Vaughn *et al.* only describe binding of the antibody to cells. Vaughn *et al.* characterize the reference to antibody BK.19.9 as being a human transferrin receptor antibody as an unpublished observation of Dr. G. Brown. *See Materials and Methods.* Importantly, later publications, including Walker *et al.* (*Immunology*, 58:583-589 (1986))(**Exhibit A**), indicate that BK.19.9 is not a transferrin receptor antibody:

> [c]oincident with the appearance of CD23, p45 was the induction of the lineage-unrestricted antigen defined by BK19.9. *Although initially suspected to share identity with the transferrin receptor, it is now clear that the antigen recognized is quite distinct.* Its function remains unknown, but its early appearance on activation, its wide tissue

> distribution and its high expression in malignancy suggest that this antigen may have an essential role in growth and survival.

Walker *et al.*, p. 587 (citations omitted)(emphasis added). Thus, Vaughn *et al.* do not teach contacting transferrin receptor with a test compound. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejection.

The Examiner rejected claims 14-15 and 19 under 35 U.S.C. § 102(b) as allegedly anticipated by Ng *et al.* (*PNAS*, 99:10706-10711 (2002))("Ng *et al.*") as evidenced by Merino *et al.* The Examiner contends that Ng *et al.* teach contacting a transferrin receptor protein expressed on the surface of cells *in vitro* with transferrin receptor antibody-avidin fusion protein and monitoring whether the transferrin receptor antibody-avidin fusion protein binds to the transferrin receptor protein. The Examiner contends that the transferrin receptor antibody-avidin fusion protein induced apoptosis while the antibody without avidin fused does not, which identifies the fusion protein as a potentially therapeutic anticancer compound. The Examiner cites Merino *et al.* as allegedly establishing that the transferrin receptor sequence is 100% identical to SEQ ID NOS:1, 2, 3 and 8. Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully assert that the claims should not be rejected under 35 U.S.C. § 102(b) over Ng *et al.* The publication date on the face of Ng *et al.* is August 6, 2002, and therefore, because it was not published more than one year prior to Applicants' provisional Application No. 60/463,649, filed April 18, 2003, it is not prior art under 35 U.S.C. § 102(b). Applicants are entitled to claim the benefit of provisional Application No. 60/463,649. Applicants note that support for claim 14 may be found in claims 10-11 as filed in Applicants' provisional Appl. No. 60/463,649 and throughout the

specification. For at least this reason, Applicants respectfully request that the Examiner withdraw the rejection.

Nonetheless, Ng *et al.* describe a transferrin antibody-avidin fusion protein that allegedly functions, like the transferrin ligand, by binding to the receptor *and entering the cell by receptor mediated endocytosis*. In contrast, the specification demonstrates that the gambogic acid binding site *interferes with transferrin receptor internalization*. *See* Fig. 2A and 2B. Thus, the compounds have opposite effects on the receptor. This is strong evidence that the binding sites are independent of one another and distinct. Thus, even if the document were prior art, which the Applicants do not concede, it will fail to anticipate the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner further rejected claims 14-15, 19-20 and 30 under 35 U.S.C. § 102(b) as allegedly anticipated by Cai *et al.* (U.S. Patent No. 6,462,041)("Cai *et al.*") as evidenced by Kasibhatla *et al.* (*PNAS*, 102(34):12095-12100 (2005))("Kasibhatla *et al.* (a)") and Merino *et al.* The Examiner contends that Cai *et al.* teach contacting cells *in vitro* with gambogic acid and monitoring cell proliferation and caspase activity in the T47D cell line to identify gambogic acid as a potentially therapeutic anticancer compound. The gist of the Examiner's argument is that, while Cai *et al.* is silent about whether gambogic acid binds to the transferrin receptor, the ability of gambogic acid to bind the transferrin receptor and cause apoptosis is an inherent property of gambogic acid, and so, by monitoring the outcome of contacting the cells with gambogic acid, *viz.*, apoptosis, Cai *et al.* is indirectly monitoring whether the compound binds the transferrin receptor and identifying it as a potentially therapeutic anticancer compound. The

Examiner relies on Kasibhatla *et al.* (a) as allegedly establishing that the T47D cell lines expresses transferrin receptor and relies on Merino *et al.* to allegedly establish that the receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8. Applicants respectfully traverse this rejection.

Applicants respectfully assert that the claims should not be rejected under 35 U.S.C. § 102(b) over Cai *et al.* Cai *et al.* issued on October 8, 2002, and therefore, because this date is not more than one year prior to Applicants' provisional Application No. 60/463,649, filed April 18, 2003, it is not prior art under 35 U.S.C. § 102(b). Applicants are entitled to claim the benefit of provisional Application No. 60/463,649. Applicants note that support for claims 14, 20 and 30 may be found in claims 10-12 and 20 as filed in Applicants' provisional Appl. No. 60/463,649 and throughout the specification. For at least this reason, Applicants respectfully request that the Examiner withdraw the rejection.

In any event, contrary to the Examiner's assertions, Cai *et al.* do not disclose, either expressly or inherently, (b) of claim 14, *viz.*, monitoring whether said one or more test compounds binds to TRRAIP. Cai *et al.* did not monitor binding to TRRAIP. The monitoring of apoptosis by Cai *et al.* in T47D cells *is not* the same thing, either expressly or inherently, as monitoring binding to TRRAIP. While the gambogic acid *may have* bound to transferrin receptor as an upstream target in the cells, a person skilled in the art would not equate the two monitoring activities. Importantly, Cai *et al. do not show a correlation to apoptosis and any binding* to TRRAIP in Cai *et al.* In the absence of such a showing of a correlation, there can be no monitoring of binding to TRRAIP under these circumstances. In contrast, Applicants specification describes assays to monitor binding

of test compounds to TRRAIP proteins. Specifically, the specification describes homogenous and heterogenous screening assays. The specification states:

> [t]hese assays may be radioassays, fluorescence polarization assays or other fluorescence techniques, or biotin-avidin based assays. Test compounds capable of binding to AIPs are candidates for activators of apoptosis. Test compounds may be capable of binding to AIPs as strongly or more strongly than gambogic acid or GA-related compounds.

Specification, paragraph [0168], p. 88. The specification also discusses certain cell-based assays. *See, e.g.*, paragraphs [0203]-[0227] at p. 102-112 of the specification. When monitoring for AIP binding to test compounds, the cell-based assays described in the specification *are designed to determine a correlation* between AIP expression level and apoptotic effects of the compounds, *e.g.*, by comparing the apoptotic effects of test compounds on cells expressing varying amounts of AIPs. In this way, a reasonable correlation can be made to AIP binding and apoptotic activity. There is no such correlative data in Cai *et al.* to reasonably establish monitoring of binding activity. A person skilled in the art would not consider treating cells with a compound and observing apoptotic effects, without more, as a readout or assay of transferrin receptor binding. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner further rejected claim 14 under 35 U.S.C. § 102(b) as allegedly anticipated by Cai *et al.* (U.S. Patent No. 6,462,041) on other grounds, as evidenced by Hinoda *et al.* The Examiner alleged that Cai *et al.* teach contacting the cells with bioconjugate test compounds comprising the antibody trastuzumab and gambogic acid related compounds. The Examiner contends that Hinoda *et al.* teach that trastuzumab

binds HER2 on the surface of cells, making HER2 an Apoptosis Inducing Protein. Applicants respectfully traverse this rejection.

Applicants respectfully assert, as above, that Cai *et al.* is not prior art under 35 U.S.C. § 102(b). For at least this reason, Applicants respectfully request that the Examiner withdraw the rejection. Nonetheless, in accordance with the restriction requirement, Applicants have amended claim 14 to recite a Transferrin Receptor Related Apoptosis Inducing Protein of SEQ ID NOS:1, 2, 3 or 8. Thus, HER2 is not recited in the claims as being an Apoptosis Inducing Protein. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner further rejected claims 14-15, 19 and 30 under 35 U.S.C. § 102(a) as allegedly anticipated by Kasibhatla *et al.* (*Clinical Cancer Research*, 9:6164S #B107 (2003))("Kasibhatla *et al.* (b)"), as evidenced by Xu *et al.* (*Molecular Cancer Therapeutics*, 1:337-346 (2002))("Xu *et al.*") and Merino *et al.* The Examiner contends that Kasibhatla *et al.* (b) teach contacting a prostate cancer cell line with MX-2167, a gambogic acid-related compound and monitoring cell proliferation in this line to identify MX-2167 as a potentially therapeutic anticancer compound. The Examiner relies on Xu *et al.* and Merino *et al.* as allegedly establishing that prostate cell lines express transferrin receptor. The Examiner contends that while Kasibhatla *et al.* (b) are silent about whether MX-2167 binds the transferrin receptor, the ability of gambogic acid-related compounds to bind transferrin receptor and cause apoptosis is an inherent property of the compounds, so by monitoring the outcome of contacting the cells, Kasibhatla *et al.* (b) is indirectly monitoring whether MX-2167 binds the transferrin receptor and identifying MX-2167 as

a potentially therapeutic anticancer compound. Applicants respectfully traverse this rejection.

Applicants respectfully assert that the claims should not be rejected under 35 U.S.C. § 102(a) over Kasibhatla *et al.* (b). The publication date on the face of Kasibhatla *et al.* (b) is December 2003, and therefore, because this date is not prior to Applicants' provisional Application No. 60/463,649, filed April 18, 2003, for at least these reasons, it is not prior art under 35 U.S.C. § 102(a). Applicants are entitled to claim the benefit of provisional Application No. 60/463,649. Applicants note that support for claims 14, 20 and 30 may be found in claims 10-12 and 20 as filed in Applicants' provisional Appl. No. 60/463,649 and throughout the specification. For at least this reason, Applicants respectfully request that the Examiner withdraw the rejection.

Nonetheless, for the same reasons that Cai *et al.* do not disclose, either expressly or inherently, monitoring whether said one or more test compounds binds to TRRAIP, Kasibhatla *et al.* (b) do not disclose this process. While the gambogic acid-related compound *may have* bound to TRRAIP as an upstream target in the cells, a person skilled in the art would not consider simply treating cells with the compound and observing apoptotic effects, without more, as a readout or assay of TRRAIP binding. There is no *correlation* of apoptosis and any binding to TRRAIP in Kasibhatla *et al.* (b). If there is no correlation established by the cited art, then it cannot be maintained that binding to TRRAIP was in any way monitored.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 14-15 and 24-45 under 35 U.S.C. 103(a) as allegedly unpatentable over Faulk in view of Shyjan (U.S. Patent No. 6,458,939). The Examiner contends that while Faulk does not expressly teach labeling the transferrin receptor protein with a fluorescent label or a radiolabel, Shyjan teach that proteins can be labeled with radiolabels or fluorescent labels to facilitate detection of complexes formed between the protein and test substances and it would have been *prima facie* obvious to label the transferrin receptor in order to facilitate detection of complexes formed between the transferrin receptor protein and test compounds. Applicants respectfully traverse this rejection.

As discussed above, Applicants have amended claim 14 to recite, *inter alia*, contacting a Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8 and a detectably labeled gambogic acid (GA) or GA-related compound with one or more test compounds. The specification demonstrates that binding of gambogic acid is not inhibited by binding of transferrin to the receptor, strongly supporting that the binding sites for transferrin and gambogic acid are independent of each other. *See* Figure 1D of the specification. Faulk only disclose contacting a transferrin receptor with labeled transferrin and does not disclose or suggest, either alone or in combination with Shyjan, contacting the receptor with a compound that competes with gambogic acid. Thus, whether or not it would have been obvious to label the transferrin receptor in order to facilitate detection of complexes is not material to the analysis.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner further rejected claims 14-15, 22-23 and 26-29 under 35 U.S.C. § 103(a) as allegedly unpatentable over Cai *et al.* in view of Kasibhatla *et al.* (b) and Shyjan. The Examiner contends that while Cai *et al.* do not expressly teach competitive heterogeneous fluorescence polarization assays or radioassays comprising a gambogic acid-related compound having a fluorescent label or radiolabel, these deficiencies are made up for in the teachings of Kasibhatla *et al.* (b) and Shyjan.

As discussed above, Cai *et al.* is not prior art to Applicants claims under 35 U.S.C. § 102(b), and moreover, does not disclose, either expressly or inherently, monitoring binding of test compounds to TRRAIP because Cai *et al.* do not make any correlation to TRRAIP and any of the apoptotic effects observed in the cells. Similarly, Kasibhatla *et al.* (b) is not prior art to Applicants' claims and is completely silent regarding a correlation to apoptosis and TRRAIP binding. If there is no correlation established by the cited art, then it cannot be maintained that binding to TRRAIP was in any way monitored. Thus, whether or not it would have been obvious to conduct competitive heterogeneous fluorescence polarization assays or radioassays comprising a gambogic acid-related compound having a fluorescent label or radiolabel is not material, because the cited art does not in any way suggest monitoring TRRAIP binding with test compounds.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Double Patenting Rejections

The Examiner rejected claim 14 on the ground of obviousness-type double patenting as allegedly unpatentable over claims 10-20 of copending application no. 11/525,140. The Examiner contends that claims 10-20 of the copending application no. 11/525,140 are drawn to methods of comprising contacting Tail Interating Protein Related Apoptosis Inducing Protein (TIPRAIP) with one or more test compounds and monitoring whether the compounds bind to said TIPRAIP. The Examiner alleges that the claims are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application. Applicants respectfully traverse this rejection.

As noted above, and in accordance with the restriction requirement, Applicants have amended claim 14 to recite Transferrin Receptor Related Apoptosis Inducing Protein (TRRAIP) encoded by SEQ ID NOS:1, 2, 3 or 8 as the apoptotic inducing protein. Accordingly, the claimed TRRAIP is defined by a different sequence than TIPRAIP and therefore claim 14 is neither the same, nor obvious in view of claims 10-20 of Appl. No. 11/525,140.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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